A Ligand-based Computational Drug Repurposing Pipeline using KNIME and Programmatic Data Access: Cases Studies for Rare Diseases and COVID-19

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Supplementary Table S1: Protein targets with potential interest for treatment of COVID-19 (available from https://covid-19.uniprot.org/uniprotkb?query=*), retrieved August 2020.

UniProt ID	Target Name	Organism	Target Shortcut
O15393	Transmembrane protease serine 2	Homo sapiens	TMPS2_HUMAN
Q92499	ATP-dependent RNA helicase DDX1	Homo sapiens	DDX1_HUMAN
Q9BYF1	Angiotensin-converting enzyme 2	Homo sapiens	ACE2_HUMAN
O43765	Small glutamine-rich tetratricopeptide repeat	Homo sapiens	SGTA_HUMAN
P20701	containing protein alpha	Homo sapiens	ITAL_HUMAN
P35232	Integrin alpha-L	Homo sapiens	PHB_HUMAN
P84022	Prohibitin	Homo sapiens	SMAD3_HUMAN
Q8N3R9	Mothers against decapentaplegic homolog 3	Homo sapiens	MPP5_HUMAN
Q99623	MAGUK p55 subfamily member 5	Homo sapiens	PHB2_HUMAN
P05231	Interleukin-6	Homo sapiens	IL6_HUMAN
P07711	Procathepsin L	Homo sapiens	CATL1_HUMAN
P08887	Interleukin-6 receptor subunit alpha	Homo sapiens	IL6RA_HUMAN
P09958	Furin	Homo sapiens	FURIN_HUMAN
P35613	Basigin	Homo sapiens	BASI_HUMAN
P40189	Interleukin-6 receptor subunit delta	Homo sapiens	IL6RB_HUMAN
P52292	Importin subunit alpha-1	Homo sapiens	IMA1_HUMAN
P62937	Peptidyl-prolyl cis-trans isomerase A	Homo sapiens	PPIA_HUMAN
Q10589	Bone marrow stromal antigen 2	Homo sapiens	BST2_HUMAN
Q16552	Interleukin-17A	Homo sapiens	IL17_HUMAN
Q8NAC3	Interleukin-17 receptor C	Homo sapiens	I17RC_HUMAN
Q8NHX9	Two pore calcium channel protein 2	Homo sapiens	TPC2_HUMAN
Q96F46	Interleukin-17 receptor A	Homo sapiens	I17RA_HUMAN
Q96PD4	Interleukin-17F	Homo sapiens	IL17F_HUMAN
Q9Y2I7	1-phosphatidylinositol 3-phosphate 5-kinase	Homo sapiens	FYV1_HUMAN
Q99623	Prohibitin-2	SARS COV	R1A_CVHSA
P0C6U8	Replicase polyprotein 1a	SARS COV	R1AB_CVHSA

P0C6X7	Replicase polyprotein 1ab	SARS COV-2	R1A_SARS2
P0DTC1	Replicase polyprotein 1a	SARS COV-2	R1AB_SARS2
P0DTD1	Replicase polyprotein 1ab	SARS COV-2	SPIKE_SARS2
P0DTC2	Spike glycoprotein	SARS COV	SPIKE_CVHSA
P59594	Spike glycoprotein	SARS COV	NCAP_CVHSA
P59595	Nucleoprotein	SARS COV	AP3A_CVHSA
P59632	Protein 3a	SARS COV	NS7A_CVHSA
P59635	Protein 7a	SARS COV	VEMP_CVHSA
P59637	Envelope small membrane protein	SARS COV	VME1_CVHSA
P59596	Membrane protein	SARS COV	NS3B_CVHSA
P59633	Non-structural protein 3b	SARS COV-2	AP3A_SARS2
P0DTC3	Protein 3a	SARS COV-2	VME1_SARS2
P0DTC5	Membrane protein	SARS COV-2	NS7A_SARS2
P0DTC7	Protein 7a	SARS COV-2	NCAP_SARS2
P0DTC9	Nucleoprotein	SARS COV	NS6_CVHSA
P59634	Non-structural protein 6	SARS COV	ORF9B_CVHSA
P59636	Protein 9b	SARS COV-2	VEMP_SARS2
P0DTC4	Envelope small membrane protein	SARS COV-2	NS6_SARS2
P0DTC6	Non-structural protein 6	SARS COV-2	ORF9B_SARS2
P0DTD2	Protein 9b	SARS COV	NS7B_CVHSA
Q7TFA1	Protein non-structural 7b	SARS COV	NS8B_CVHSA
Q80H93	Non-structural protein 8b	SARS COV-2	NS8_SARS2
P0DTC8	Non-structural protein 8	SARS COV-2	Y14_SARS2
P0DTD3	Uncharacterized protein 14	SARS COV-2	NS7B_SARS2
P0DTD8	Protein non-structural 7b	SARS COV	NS8A_CVHSA
Q7TFA0	Protein non-structural 8a	SARS COV	Y14_CVHSA
Q7TLC7	Uncharacterized protein 14	SARS COV-2	A0A663DJA2_SARS2
A0A663DJA2	ORF10 protein		

Supplementary Table S2: Protein targets with potential interest for treatment of COVID-19 retrieved from the Open Targets Platform; retrieved in September 2020.

Uniprot ID	Target Name	Organism	Target Shortcut
P34903	gamma-aminobutyric acid type A receptor subunit alpha3	Homo Sapiens	GABRA3_HUMAN
P14867	gamma-aminobutyric acid type A receptor subunit alpha1	Homo Sapiens	GABRA1_HUMAN
P35354	prostaglandin-endoperoxide synthase 2	Homo Sapiens	PTGS2_HUMAN
O95069	potassium two pore domain channel subfamily K member 2	Homo Sapiens	KCNK2_HUMAN
O00591	gamma-aminobutyric acid type A receptor subunit pi	Homo Sapiens	GABRP_HUMAN
P23219	prostaglandin-endoperoxide synthase 1	Homo Sapiens	PTGS1_HUMAN
P62877	ring-box 1	Homo Sapiens	RBX1_HUMAN
P57789	potassium two pore domain channel subfamily K member 10	Homo Sapiens	KCNK10_HUMAN
Q9H4B7	tubulin beta 1 class VI	Homo Sapiens	TUBB1_HUMAN
P78334	gamma-aminobutyric acid type A receptor subunit epsilon	Homo Sapiens	GABRE_HUMAN
P04350	tubulin beta 4A class IVa	Homo Sapiens	TUBB4A_HUMAN
P48169	gamma-aminobutyric acid type A receptor subunit alpha4	Homo Sapiens	GABRA4_HUMAN
P18507	gamma-aminobutyric acid type A receptor subunit gamma2	Homo Sapiens	GABRG2_HUMAN
P04150	nuclear receptor subfamily 3 group C member 1	Homo Sapiens	NR3C1_HUMAN
Q96SW2	cereblon	Homo Sapiens	CRBN_HUMAN
P14778	interleukin 1 receptor type 1	Homo Sapiens	IL1R1_HUMAN
P01008	serpin family C member 1	Homo Sapiens	SERPINC1_HUMA

P22894	matrix metallopeptidase 8	Homo Sapiens	MMP8_HUMAN
Q13885	tubulin beta 2A class IIa	Homo Sapiens	TUBB2A_HUMAN
Q9BVA1	tubulin beta 2B class IIb	Homo Sapiens	TUBB2B_HUMAN
P09237	matrix metallopeptidase 7	Homo Sapiens	MMP7_HUMAN
P45452	matrix metallopeptidase 13	Homo Sapiens	MMP13_HUMAN
Q13619	cullin 4A	Homo Sapiens	CUL4A_HUMAN
P17181	interferon alpha and beta receptor subunit 1	Homo Sapiens	IFNAR1_HUMAN
P30556	angiotensin II receptor type 1	Homo Sapiens	AGTR1_HUMAN
Q16445	gamma-aminobutyric acid type A receptor subunit alpha6	Homo Sapiens	GABRA6_HUMAN
P47870	gamma-aminobutyric acid type A receptor subunit beta2	Homo Sapiens	GABRB2_HUMAN
P23415	glycine receptor alpha 1	Homo Sapiens	GLRA1_HUMAN
P08913	adrenoceptor alpha 2A	Homo Sapiens	ADRA2A_HUMAN
P47869	gamma-aminobutyric acid type A receptor subunit alpha2	Homo Sapiens	GABRA2_HUMAN
P48551	interferon alpha and beta receptor subunit 2	Homo Sapiens	IFNAR2_HUMAN
P08887	interleukin 6 receptor	Homo Sapiens	IL6R_HUMAN
Q8N1C3	gamma-aminobutyric acid type A receptor subunit gamma1	Homo Sapiens	GABRG1_HUMAN
P18505	gamma-aminobutyric acid type A receptor subunit beta1	Homo Sapiens	GABRB1_HUMAN
P28472	gamma-aminobutyric acid type A receptor subunit beta3	Homo Sapiens	GABRB3_HUMAN
Q16531	damage specific DNA binding protein 1	Homo Sapiens	DDB1_HUMAN

Q9NPC2	potassium two pore domain channel subfamily K member 9	Homo Sapiens	KCNK9_HUMAN
P06213	insulin receptor	Homo Sapiens	INSR_HUMAN
O14649	potassium two pore domain channel subfamily K member 3	Homo Sapiens	KCNK3_HUMAN
Q9BUF5	tubulin beta 6 class V	Homo Sapiens	TUBB6_HUMAN
Q99928	gamma-aminobutyric acid type A receptor subunit gamma3	Homo Sapiens	GABRG3_HUMAN
P18825	adrenoceptor alpha 2C	Homo Sapiens	ADRA2C_HUMAN
P31644	gamma-aminobutyric acid type A receptor subunit alpha5	Homo Sapiens	GABRA5_HUMAN
Q7Z418	potassium two pore domain channel subfamily K member 18	Homo Sapiens	KCNK18_HUMAN
O14764	gamma-aminobutyric acid type A receptor subunit delta	Homo Sapiens	GABRD_HUMAN
P68371	tubulin beta 4B class IVb	Homo Sapiens	TUBB4B_HUMAN
P07437	tubulin beta class I	Homo Sapiens	TUBB_HUMAN
P03956	matrix metallopeptidase 1	Homo Sapiens	MMP1_HUMAN
Q9NYK1	toll like receptor 7	Homo Sapiens	TLR7_HUMAN
P27487	dipeptidyl peptidase 4	Homo Sapiens	DPP4_HUMAN
P15509	colony stimulating factor 2 receptor subunit alpha	Homo Sapiens	CSF2RA_HUMAN
Q9NR96	toll like receptor 9	Homo Sapiens	TLR9_HUMAN
Q13509	tubulin beta 3 class III	Homo Sapiens	TUBB3_HUMAN
Q3ZCM7	tubulin beta 8 class VIII	Homo Sapiens	TUBB8_HUMAN
P18089	adrenoceptor alpha 2B	Homo Sapiens	ADRA2B_HUMAN

Supplementary Table S3: Number of unique ligands gathered from PDB, ChEMBL, PubChem, and IUPHAR for COVID-19 targets from UniProt pre-release web page.

Target shortcut	PDB	ChEMBL	IUPHAR	PubChem	# Unique active compounds
PPIA_HUMAN	57	2	1	3123	3183
CATL1_HUMAN	25	38	4	946	1003
ITAL_HUMAN	13	94	2	550	564
FURIN_HUMAN	4	10	1	448	463
R1AB_CVHSA	37	187	0	47	227
ACE2_HUMAN	4	65	3	161	172
R1A_CVHSA	35	92	0	79	141
SMAD3_HUMAN	3	64	0	65	71
IL6_HUMAN	3	0	0	13	16
DDX1_HUMAN	0	7	0	7	14
R1AB_SARS2	14	0	0	0	9
TMPS2_HUMAN	2	3	4	3	7
IL17_HUMAN	7	0	0	0	7
SPIKE_SARS2	5	0	0	0	5
SPIKE_CVHSA	5	0	0	0	5
BST2_HUMAN	5	0	0	0	5
IL6RB_HUMAN	4	0	0	0	4

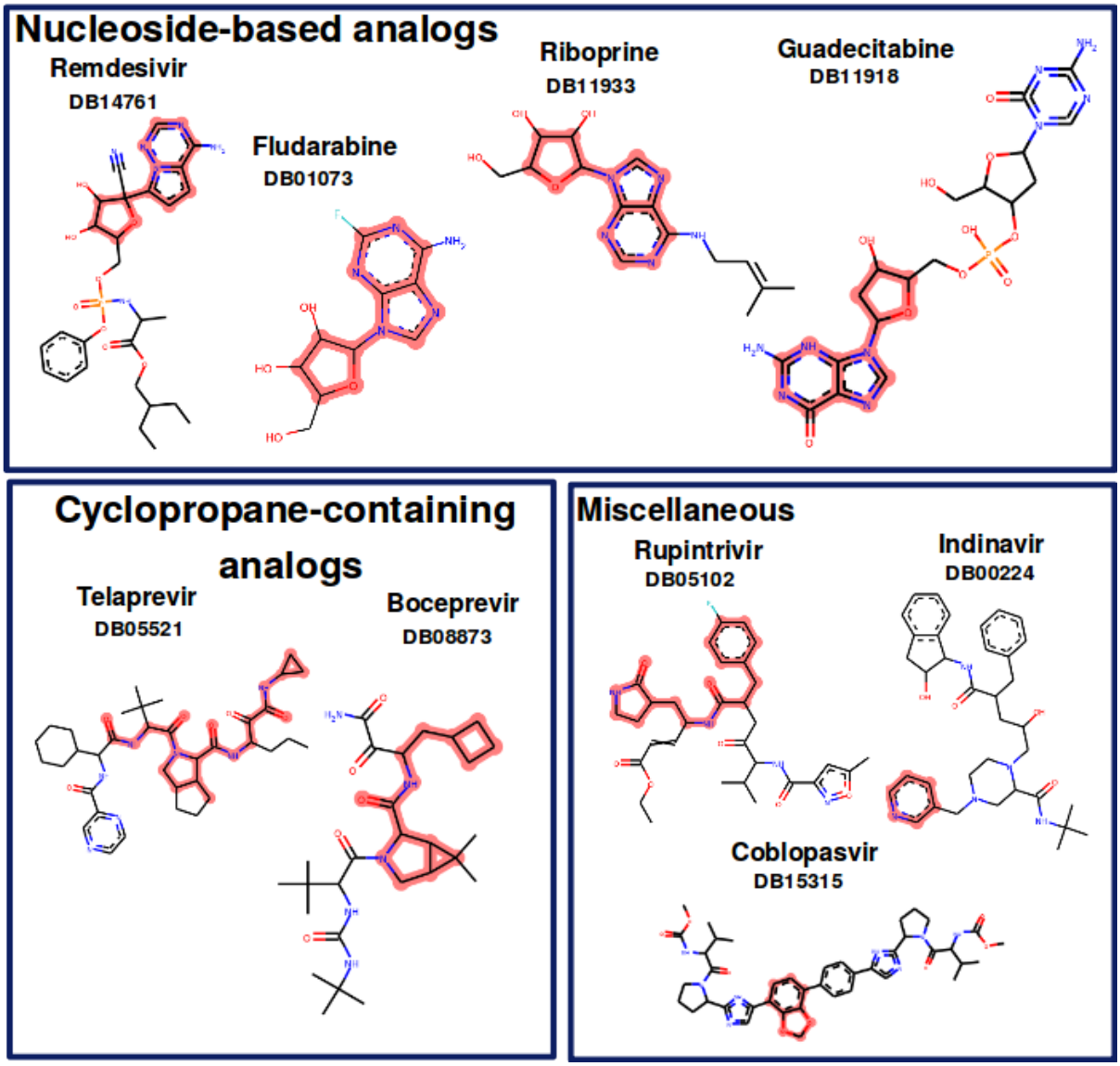
BASI_HUMAN	3	0	0	0	3
IMA1_HUMAN	3	0	0	0	3
IL17F_HUMAN	3	0	0	0	3
SGTA_HUMAN	2	0	0	0	2
R1A_SARS2	2	0	0	0	2
VME1_CVHSA	2	0	0	0	2
IL6RA_HUMAN	2	0	0	0	2
I17RC_HUMAN	1	0	1	0	2
I17RA_HUMAN	2	0	0	0	2
MPP5_HUMAN	1	0	0	0	1
ORF9B_CVHSA	1	0	0	0	1
I17RC_HUMAN	1	0	0	0	1
FYV1_HUMAN	0	0	1	0	1

Supplementary Table S4: Number of unique ligands gathered from PDB, ChEMBL, PubChem, and IUPHAR for COVID-19 targets from the Open Targets Platform.

Target shortcut	ChEMBL	IUPHAR	PubChem	PDB	# Unique active compounds
GABRG2_HUMAN	152	0	677	2	831
MMP13_HUMAN	319	3	80	28	430
GABRB1_HUMAN	121	0	166	0	287
DPP4_HUMAN	140	2	29	14	185
GABRA1_HUMAN	3	4	172	2	181
ADRA2C_HUMAN	60	19	99	0	178
AGTR1_HUMAN	111	14	34	1	160
MMP1_HUMAN	57	1	65	9	132
MMP8_HUMAN	81	2	12	18	113
TUBB2A_HUMAN	53	0	56	0	109
GABRG1_HUMAN	49	0	52	0	101
GABRP_HUMAN	46	0	54	0	100
NR3C1_HUMAN	79	8	0	1	88
GABRE_HUMAN	38	0	46	0	84
ADRA2A_HUMAN	47	13	13	0	73
GABRG3_HUMAN	33	0	35	0	68
GABRB2_HUMAN	0	0	65	1	66
GABRD_HUMAN	0	0	48	0	48

TUBB2B_HUMAN	20	0	20	3	43
ADRA2B_HUMAN	11	14	16	0	41
GABRA5_HUMAN	33	4	0	1	38
TUBB_HUMAN	0	0	33	3	36
TUBB6_HUMAN	15	0	15	0	30
PTGS2_HUMAN	23	0	4	2	29
INSR_HUMAN	4	3	10	9	26
TUBB4A_HUMAN	0	0	23	0	23
TUBB3_HUMAN	0	0	18	4	22
GLRA1_HUMAN	4	7	2	1	14
MMP7_HUMAN	4	2	0	8	14
CRBN_HUMAN	1	7	2	1	11
KCNK9_HUMAN	1	0	5	4	10
GABRA2_HUMAN	4	4	0	0	8
TUBB1_HUMAN	0	0	8	0	8
PTGS1_HUMAN	1	5	1	0	7
TUBB4B_HUMAN	0	0	7	0	7
KCNK2_HUMAN	0	2	0	3	5
SERPINC1_HUMAN	0	2	0	3	5
TLR7_HUMAN	3	1	1	0	5
KCNK10_HUMAN	0	1	0	2	3

KCNK3_HUMAN	0	2	0	1	3
DDB1_HUMAN	0	0	0	2	2
GABRB3_HUMAN	0	0	0	2	2
IL1R1_HUMAN	0	0	0	2	2
IL6R_HUMAN	0	0	0	2	2
CSF2RA_HUMAN	0	0	0	1	1
CUL4A_HUMAN	0	0	0	1	1
GABRA4_HUMAN	1	0	0	0	1
IFNAR1_HUMAN	0	0	0	1	1
IFNAR2_HUMAN	0	0	0	1	1
RBX1_HUMAN	0	0	0	1	1



Supplementary Figure 1: *Examples of identified drugs with structural queries highlighted..*

Description of Supplementary Data Files:

Supplementary File S1: CSV file with maximum common substructures in SMARTS format (n= 257) detected via hierarchical scaffold clustering for the COVID-19 use case (available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Supplementary_file1.csv)

Supplementary File S2: CSV file with identified hits for COVID-19 from DrugBank (n=7,836; available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Supplementary_file2.csv)

Supplementary File S3: CSV file with identified hits for COVID-19 from CAS Dataset (n=36,521; available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Supplementary_file3.csv)

Supplementary File S4: CSV file with identified for COVID-19 hits by both DrugBank and CAS Dataset (n=228; available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Supplementary_file4.csv)

Supplementary File S5: CSV file with identified hits for GLUT-1 deficiency syndrome from DrugBank (n=539; available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Supplementary_file5.csv)

Supplementary File S6: KNIME drug repurposing workflow (KNWF file) where external UniProt dataset is used as an input(available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/DrugRepurposingPipeline_UniProt.knwf)

Supplementary File S7: KNIME drug repurposing workflow (KNWF file) where disease-target associations from the OpenTarget platform are used an input (available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/DrugRepurposingPipeline_OpenTargets.knwf)

Supplementary File S8: A .pdf Tutorial file “Part 1: Programmatic access to UniProt database using KNIME” (available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Part1.pdf)

Supplementary File S9: A .pdf Tutorial file “Part 2: Using cross-references to retrieve structural data from the Protein Data Bank (PDB)” (available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Part2.pdf)

Supplementary File S10: A .pdf Tutorial file "Part 3: Integrative data mining of ligand bioactivity data from ChEMBL and PubChem" (available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Part3.pdf)

Supplementary File S10: A .pdf Tutorial file "Part 4: Substructure searches in DrugBank" (available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Part4.pdf)

Supplementary File S11 A .pdf Tutorial file with the answer sheet (available at https://github.com/AlzbetaTuerkova/Drug-Repurposing-in-KNIME/blob/master/Answersheet.pdf)